AMENDED SPECIFICATION

Reprinted as amended under Section 8 of the Patents Act, 1949.

PATENT SPECIFICATION

1,038,529

NO DRAWINGS

1,038,529

Date of Application and filing Complete Specification: March, 15 1965.

No. 10960/65.

Application made in Japan (No. 14274) on March 14, 1964.

Application made in Japan (No. 42131) on July 23, 1964.

Complete Specification Published: Aug. 10, 1966.

Index at acceptance:—C2 A(1C2A, 1C2C, 2E)

Int. Cl.:—C 07 d 99/24

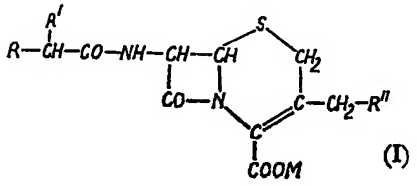
COMPLETE SPECIFICATION

7-(α-Substituted acylamino) cephalosporanic acid and derivatives thereof

We, FUJISAWA PHARMACEUTICAL CO. LTD., a Japanese Company of 3, Doshomachi 4-chome, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 7-(α-substituted acylamino) cephalosporanic acid and derivatives thereof, which compounds are useful as antimicrobial agents.

The compounds of this invention may be represented by the following general formula:



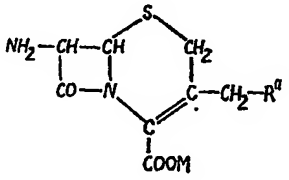
(I)

wherein R is a halogen atom or an azido (N_3), carbamoyl, lower alkylthio, lower alkanoyl, lower alkanoyloxy, lower alkoxy-lower alkoxy, lower alkoxyaralkyl, naphthoxy, halonaphthoxy, ethoxycarbonyl, arylthio or haloarylthio group or a phenoxy group having lower alkenyl and lower alkoxy substituents, R′ is an aryl, haloaryl, nitroaryl, aryloxy or arylthio group, R″ is an acetoxy, pyridinium, imidazolinium or methylimidazolinium group and M is a hydrogen atom, a pharmaceutically acceptable non-toxic cation or an anionic charge.

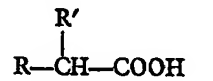
As used herein and in the claims the term "lower" is intended to mean groups containing one to six carbon atoms.

In the above formula (I), when R is lower alkanoyl it includes acetyl, propionyl or butyloyl, when R′ is aryl it includes phenyl, naphthyl or tolyl, and when M is a pharmaceutically acceptable non-toxic cation it includes an alkali metal ion such as the sodium ion or potassium ion, the ammonium radical and an organic quaternary ammonium cation such as triethylammonium, dicyclohexylammonium, diphenylenediammonium or dibenzylethylenediammonium.

The compound of formula (I) of this invention may be prepared by reacting 7-aminocephalosporanic acid or a derivative thereof having the general formula:



with an α-substituted carboxylic acid having the general formula



(III)

or a reactive derivative thereof,

wherein R, R′, R″ and M have the same meanings as defined for formula (I).

7-Aminocephalosporanic acid (7 - amino-3 - acetoxymethyl - 3 - cephem - 4 - carboxylic acid) which is one of the starting materials of formula (II) is a known compound and can be obtained by the hydrolysis of the antibiotic cephalosporin C [Biochemical Journal *79*, 408—416 (1961)].

When using an α-substituted carboxylic acid, the reaction is preferably carried out in

[*Pric*

the presence of a condensing agent such as dicyclohexylcarbodiimide, N - cyclohexyl-N - morpholinoethyl - carbodiimide, pentamethyleneketen - N - cyclohexylimine, N-ethyl - *o* - phenyl - isoxazolium - 3′ - sulphonate or phosphorus trichloride. Under such circumstances, it is believed that the reaction may mainly proceed through an active form of the carboxyl radical in the α-substituted carboxylic acid or of the amino radical in the 7-aminocephalosporanic acid.

Examples of reactive derivatives of the α-substituted carboxylic acid are the acid halide, acid anhydride, acid amide and acid ester. Examples of the reactive derivatives of the α-substituted carboxylic acid to be frequently used are the acid chloride, acid azide, mixed acid anhydride with alkylphosphoric acid or alkylcarbonic acid, acid amide with imidazole or 4-substituted imidazole, acid cyanomethyl ester and acid *p*-nitrophenyl ester. These reactive derivatives are suitably selected in accordance with the particular α-substituted carboxylic acid to be used.

The reaction is usually carried out in the presence of a solvent. As a suitable solvent may be mentioned acetone, dioxane, acetonitrile, chloroform, ethylene chloride, tetrahydrofuran, or other organic solvents which are inert in the reaction and are used commonly. Of these solvents, the hydrophylic ones may be used with water.

Also, the reaction may be carried out in the presence of a base such as an alkali metal hydrogen carbonate, trialkylamine or pyridine. The reaction is carried out in most cases under cooling or at room temperature though the temperature is not particularly limited.

After completion of the reaction, the reaction product is separated according to conventional methods known in the art.

When using the compound of formula (II) wherein M is a pharmaceutically acceptable non-toxic cation as a starting compound, a product of formula (I) wherein M is hydrogen is mainly obtained, because dissociation of the cation tends to occur during the separation of the reaction product. Therefore, if it is desired to obtain a product of formula (I) wherein M is a pharmaceutically acceptable non-toxic cation, the compound of formula (I) wherein M is hydrogen is treated with an alkali metal hydroxide, alkali metal salt of a higher fatty acid or an organic amine such as sodium hydroxide, potassium hydroxide, sodium α-ethylhexanoate, triethylamine, dicyclohexylamine, diphenylenediamine or dibenzylethylene diamine.

In addition, the compound of formula (I) wherein R″ is pyridinium, amino-pyridinium, imidazolinium or methylimidazolinium may be obtained by reacting the compound of formula (II) wherein R″ is acetoxy, with pyridine, aminopyridine, imidazole or methyl imidazole.

Both 7-aminocephalosporanic acid or its derivatives of formula (II) to be used in the reaction of this invention and the product compound of formula (I) are comparatively unstable and tend to decompose during the reaction. Therefore, it is preferable to carry out the reaction and separation under mild conditions.

The resulting compound of formula (I) not only demonstrates resistance to penicillinase but exhibits advantageous physiological properties and activity against a wide variety of micro-organisms.

The following examples will illustrate the compounds available in accordance with this invention.

In the examples, "MIC" means a minimum inhibitory concentration which is measured by the serial dilution method commonly employed in testing antimicrobial compounds, and *Escherichia coli* and *Staphylococcus aureus* are referred to as "*E. coli*" and "*St. aureus*", respectively.

EXAMPLE 1.

7-(2-Chloro-2-phenylacetamido) cephalosporanic acid:

To a solution of 540 mg. of 7-aminocephalosporanic acid and 200 mg. of sodium bicarbonate in 20 cc of acetone, was added 390 mg. of 2-chloro-2-phenylacetyl chloride in 5 cc of acetone under ice-cooling. This solution was stirred for an hour under ice-cooling and then for 3 hours at room temperature and allowed to stand overnight. After adjusting to a pH of 2.0, the reaction mixture was condensed under reduced pressure to obtain a precipitate, which was collected by filtration. The precipitate was washed with ether and dissolved in acetone to obtain 550 mg. of 7 - (2 - chloro - 2 - phenylacetamido) cephalosporanic acid as crystals having m.p. 92° to 94°C.

Analysis: Calculated for $C_{18}H_{17}O_6N_2SCl$ C 48.81, H 4.29,
Found C 48.92, H 4.31.

UV: $\lambda_{max}^{80\%\ C_2H_5OH}$ 263.5 mμ, 175.5.

MIC: *E.coli* 10γ/cc., *St.aureus* 0.25 γ/cc.

EXAMPLE 2.

7-(2-Bromo-2-phenylacetamido) cephalosporanic acid:

2-Bromo-2-phenylacetyl chloride prepared from 500 mg. of 2 - bromo - 2 - phenylacetic acid and thionyl chloride, was dissolved in 5 cc of chloroform. This solution was added to 540 mg. of 7-aminocephalosporanic acid in 25 cc. of chloroform and 0.6 cc. of triethylamine under ic-cooling and stirred for an hour. The reaction mixture was adjusted to pH 2.0 with water and hydrochloric acid, and the resulting precipitate was filtered off. The filtrate was condensed under reduced pressure and after washing with ligroin, dissolved in acetone, to which was further added water to obtain 146 mg. of 7 - (2 - bromo - 2 - phenylacetamido) cephalosporanic acid as crystals having m.p. 141° to 142°C.

MIC: *E.Coli* 10γ/cc., *St.aureus* 0.5 γ/cc.

EXAMPLE 3.

7-[2-Chloro-2-(*p*-chlorophenyl) acetamido] cephalosporanic acid:

To a chloroform solution of 600 mg. of 7-aminocephalosporanic acid and 0.6 cc. of triethylamine, was added 450 mg. of 2 - chloro-2 - (*p* - chlorophenyl) - acetylchloride under ice-cooling and the mixture was stirred for three hours under ice-cooling. The reaction mixture was adjusted to a pH of 2.0 with water and hydrochloric acid and extracted with chloroform. The extract solution was condensed under reduced pressure and to the remainder was added aqueous sodium bicarbonate solution. The water layer was adjusted to a pH of 2.0 with hydrochloric acid and treated with ether. The resulting precipitate 7 - [2 - chloro - 2 - (*p* - chlorophenyl) acetamido] cephalosporanic acid having m.p. 104° to 108°C. Furthermore, the identical substance was obtained by condensation of the ether extract solution. Total yield was 150 mg.

UV: $\lambda_{inf.}^{80\%\ C_2H_5OH}$ 264 mμ, E 95.

PPC: Rf 0.77 (Butanol: Ethanol: Water = 4:1:5, by Upper layer, ascending method.)

Rf 0.97 (Butanol: Pyridine: Water = 1:1:1 by Ascending method.)

MIC: *E.coli* >40 γ/cc., *St. aureus* 0.25 γ/cc.

EXAMPLE 4.

7-[2-Chloro-2-(*p*-bromophenyl) acetamido] cephalosporanic acid:

To a chloroform solution of 540 mg. of 7-aminocephalosporanic acid and 0.6 cc of triethylamine, was added 540 mg. of 2-chloro-2-(*p*-bromophenyl) acetyl chloride under ice-cooling and the mixture was stirred for four hours under ice-cooling. After adjusting to a pH of 2.0 with water and hydrochloric acid, the reaction mixture was condensed under reduced pressure. The remainder was washed with ether and dissolved in the sodium bicarbonate solution. This solution was further adjusted to a pH of 4.0 and the resulting precipitate was reprecipitated from a mixture of acetone and water to obtain 232 mg. of 7 - [2 - chloro - 2 - (*p* - bromophenyl) acetamido] cephalosporanic acid as hydroscopic powder having m.p. 127° to 130°C (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 262 mμ, E 112.

PPC: Rf 0.77 (Butanol: Ethanol: Water = 4:1:5, by Upper layer, ascending method)

Rf 0.80 (Butanol: Pyridine: Water = 1:1:1 by Ascending method)

MIC: *E.coli* >40 γ/cc., *St.aureus* 0.25 γ/cc.

EXAMPLE 5.

7-[2-Bromo-2-(*p*-chlorophenyl) acetamido] cephalosporanic acid:

To 838 mg of 2-bromo-2-(p-chlorophenyl) acetyl chloride dissolved into 10 cc. of chloroform, was added 820 mg of 7-aminocephalosporanic acid in 0.8 cc of triethylamine and 25 cc of chloroform and the mixture was stirred for 30 minutes under ice-cooling and then for 1.5 hours at room temperature, after which it was allowed to stand overnight in a cold place. The reaction mixture was adjusted to a pH of 1.0 with hydrochloric acid and the chloroform layer separated out was condensed under reduced pressure, The remainder was washed with ether to obtain 612 mg. of 7 - [2 - bromo - 2 - (*p* - chlorophenyl)-acetamido] cephalosporanic acid as a powder m.p. 85° to 92°C. (dec.).

MIC: *E.coli* >40 γ/cc., *St.aureus* 1 γ/cc.

EXAMPLE 6.

7-[2-Chloro-2-(*p*-nitrophenyl) acetamido] cephalosporanic acid:

A solution of 680 mg. of 7-aminocephalosporanic acid and 600 mg. of 2-chloro-2-(*p*-nitrophenyl) acetylchloride in 1.2 cc of triethylamine and 25 cc. of chloroform was stirred for 5 hours under ice-cooling. The reaction mixture was adjusted to a pH of 2.0 with hydrochloric acid and the resulting precipitate was separated out from the chloroform layer. The precipitate was extracted with acetone and, after condensing the extract solvent, the remainder was washed with ether to obtain 412 mg. of 7-[2-chloro-2-(*p*-nitrophenyl)acetamido] cephalosporanic acid as a hygroscopic powder having m.p. 60° to 63°C. (dec.). (From the remainder in acetone extraction, the 7-amino-cephalosporanic acid of the starting material was recovered.) Furthermore, 320 mg of the desired compound was obtained by condensing the chloroform layer and then washing the remainder with petroleum ether.

MIC: *E.coli* >40 γ/cc., *St.aureus* 2.5 γ/cc.

EXAMPLE 7.

7-[2-Bromo-2-(1-naphthyl) acetamido] cephalosporanic acid:

7-Aminocephalosporanic acid (680 mg.) and 1.18 g. of 2-bromo-2-(1-naphthyl) acetyl chloride were dissolved in 1.3 cc. of triethylamine and 25 cc. of chloroform and the mixture was stirred for an hour under ice-cooling. The reaction mixture was adjusted to a pH of 2.0 with hydrochloric acid and the resulting precipitate was filtered off. From the filtrate the solvent was distilled off under reduced pressure and the remainder washed with ether to obtain 625 mg. of 7-[2-bromo-2-(1-naphthyl) acetamido] cephalosporanic acid as a powder having m.p. 115° to 125°C (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH}$ 227 mμ, E 757; 295 mμ, 158.

MIC: *Eo.coli* >40 γ/cc., *St.aureus* 2.5 γ/cc.

EXAMPLE 8:

7-[2-Azido-2-(*p*-chlorophenyl) acetamido] cephalosporanic acid:

2-Azido-2-(*p*-chlorophenyl) acetic acid (555 mg.) and 2 cc. of thionyl chloride were stirred for 2 hours at 60°C and the excess of thionyl chloride was distilled off to obtain 2-azido-2-(*p*-chlorophenyl) acetyl chloride, which was dissolved in 5 cc of acetone. 7-Aminocephalosporanic acid (682 mg.) and 220 mg. of sodium bicarbonate in 10 cc. of acetone and 10 cc. of water were cooled to 0° to 5°C, to which solution was added the acetone solution of 2-azido-2-(*p*-chlorophenyl) acetyl chloride over a period of 15 minutes. The reaction mixture was stirred for 30 minutes at 0° to 5°C and then for 2 hours at room temperature, after which it was washed with ether. The water layer was adjusted to a pH of 1.0 with 5% hydrochloric acid and extracted with ethyl acetate. The solvent was distilled off under reduced pressure and the remainder was dissolved in acetone, which was distilled off. To the remaining oily substance was added ether to obtain 132 mg. of 7-[2-azido-2-(*p*-chlorophenyl)acetamido] cephalosporanic acid as a powder having m.p. 200°C. (dec.).

UV: $\lambda_{min}^{80\%\ C_2H_5OH\ .\ NaOH}$ the longest wave-length.

MIC: *E.coli* >40 γ/cc., *St.aureus* 0.5 γ/cc.

EXAMPLE 9.

7-[2-Azido-2-(*p*-nitrophenyl) acetamido] cephalosporanic acid:

2-Azido-2-(*p*-nitrophenyl) acetic acid (555 mg.) and 1.1 cc. of thionyl chloride were stirred for 2 hours at 60°C. and the excess of thionyl chloride was distilled off to obtain 2-azido-2-(*p*-nitrophenyl) acetyl chloride, which was dissolved in acetone. 7-Aminocephalosporanic acid (682 mg.) and 220 mg. of sodium bicarbonate in 15 cc. of acetone and 15 cc. of water were cooled to 0° to 5°C., to which solution was added drop by drop the acetone solution of 2-azido-2-(*p*-nitrophenyl) acetyl chloride above prepared over a period of 15 minutes. The reaction mixture was stirred for 30 minutes at 0° to 5°C. and allowed to stand for one day. The reaction mixture was washed with ether and, after adjusting the water layer at a pH of 2.0 with 5% hydrochloric acid, extracted with ethyl acetate. The solvent was distilled off under reduced pressure and to the remaining oily substance was added petroleum ether to obtain 331 mg. of 7-[2-azido-2-(*p*-nitrophenyl) acetamido] cephalosporanic acid as a powder having m.p. 175° to 180°C (dec.). (From the mother liquid, 207 mg. of 7-aminocephalosporanic acid was recovered.)

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 272 mμ, E 276.

EXAMPLE 10.
7-(2-Acetoxy-2-phenylacetamido) cephalosporanic acid:

To a solution of 540 mg. of 7-aminocephalosporanic acid and 300 mg. of triethylamine in 30 cc. of chloroform, was added 425 mg of 2-acetoxy-2-phenylacetyl chloride in 5 cc of chloroform under ice-cooling. This solution was stirred for 2 hours under ice-cooling and then for 4 hours at room temperature and allowed to stand overnight. The reaction mixture was filtered, after which to the filtrate was added dilute sulphuric acid and the mixture was extracted with chloroform. The extract solution was condensed under reduced pressure, and the remainder was washed with ether and dissolved in acetone. To this acetone solution was added ether and the solution was allowed to stand to obtain 250 mg. of 7-(2-acetoxy-2-phenylacetamido) cephalosporanic acid as a hygroscopic powder having m.p. 92° to 96°C.

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 231.5 mμ, E 358; 260 mμ, E 118

PPC: Rf 0.72 (Butanol: Ethanol: Water = 4:1:5, by Upper layer, ascending method)
Rf 0.79 (Butanol: Pyridine: Water = 1:1:1 by Ascending method)

MIC: *E.coli* 20 γ/cc., *St.aureus* 5 γ/cc.

EXAMPLE 11.
7-(2-Methylthio-2-phenylacetamido) cephalosporanic acid:

To 327 mg. of 2-methylthio-2-phenylacetic acid in 5 cc. of tetrahydrofuran was added 400 mg. of dicyclohexylcarbodiimide in 2 cc. of tetrahydrofuran and the mixture was stirred for 15 minutes at room temperature. To this solution was added the chloroform solution containing 500 mg. of 7-aminocephalosporanic acid and 0.25 cc. of triethylamine and after stirring for 3 hours at room temperature, the mixture was allowed to stand overnight. To the reaction mixture was added water to produce the decomposed product of dicyclohexylcarbodiimide which was removed by filtration. The water layer was adjusted to a pH of 1.0 with 5% hydrochloric acid and extracted with ethyl acetate. The solvent was distilled off under reduced pressure and to the remainder was added petroleum ether to obtain 416 mg. of 7-(2-methylthio-2-phenylacetamido) cephalosporanic acid as a powder having m.p. 78° to 84°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH}$ 262 mμ, E 164.

MIC: *E.coli* 20 γ/cc., *St.aureus* 1 γ/cc.

EXAMPLE 12.
7-(2-Acetyl-2-phenylacetamido) cephalosporanic acid:

To 320 mg. of 2-acetyl-2-phenylacetic acid in 15 cc. of tetrahydrofuran was added 370 mg. of dicyclohexylcarbodiimide in 1.7 cc of tetrahydrofuran and the mixture was stirred for 20 minutes at room temperature. To this solution was added 10 cc. of an aqueous solution containing 500 mg. of 7-aminocephalosporanic acid and 152 mg. of sodium bicarbonate and the mixture was allowed to stand overnight. The reaction mixture was filtered and tetrahydrofuran was distilled off under reduced pressure. The remainder was dissolved in water and, after adjusting to a pH of 1.0 with 5% hydrochloric acid, extracted with etheyl acetate. The extract solution was condensed under reduced pressure and the remainder was washed with ether to obtain 10 mg. of 7-(2-acetyl-2-phenylacetamido) cephalosporanic acid as a powder having m.p. 180° to 210°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH}$ 260 mμ, E 213.

MIC: *E.coli* >40 γ/cc., *St. aureus* 20 γ/cc.

EXAMPLE 13.
7-(2-Propylthio-2-phenylacetamido) cephalosporanic acid:

To 387 mg. of 2-propylthio--2phenylacetic acid dissolved in 10 cc. of tetrahydrofuran was added 400 mg. of dicyclohexylcarbodiimide in 2 cc. of tetrahydrofuran and the mixture was stirred for 15 minutes at room temperature. To this solution was added 10 cc. of an aqueous solution containing 500 mg. of 7-aminocephalosporanic acid and 150 mg. of sodium bicarbonate and, after stirring for 3.5 hours at room temperature, the mixture was allowed stand overnight. The reaction mixture was filtered and tetrahydrofuran was distilled off from the filtrate under reduced pressure. The remainder from which an oily substance was removed by decantation, was adjusted to a pH of 1.0 with hydrochloric acid and extracted with 500 cc. of ethyl acetate twice. Ethyl acetate was distilled off from the extract solution under reduced pressure and the remainder was dissolved in acetone, after which acetone was distilled off. To the remainder was added petroleum ether to obtain 266 mg. of 7-(2-propylthio-2-

phenylacetamido) cephalosporanic acid as a powder having m.p. 68° to 70°C.

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 262 mμ, E 108.

MIC: *E.coli* 40 γ/cc., *St.aureus* 0.5 γ/cc.

EXAMPLE 14.

7-[2-Phenyl-2-(*o*-bromophenylthio) acetamido] cephalosporanic acid:

2 - Phenyl - 2 - (*o* - bromophenylthio) acetic acid (650 mg.) and 230 mg. of dicyclohexylcarbodiimide were dissolved in 20 cc. of tetrahydrofuran and stirred. To this solution was added drop by drop 540 mg. of 7-aminocephalosporanic acid and 180 mg. of sodium bicarbonate in 10 cc. of tetrahydrofuran and 15 cc. of water and after stirring for 5 hours at room temperature, the mixture was allowed to stand overnight. The reaction mixture was filtered off and to the filtrate was added water. This solution was adjusted to a pH of 7.0 with sodium bicarbonate solution and filtered. To the filtrate was added ethyl acetate and the mixture was adjusted to a pH of 3.5 with hydrochloric acid, after which the water layer separated out, was adjusted to a pH of 1.0 with hydrochloric acid and extracted with ethyl acetate. From the extract solution ethyl acetate was distilled off under reduced pressure and the remainder was washed with ether to obtain 17 mg. of 7-[2-phenyl-2-(*o*-bromophenylthio) acetamido] cephalosporanic acid as a powder having m.p. 164° to 167°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 257 mμ, E 218.

MIC: *E.coli* 40 γ/cc., *St.aureus* 5 γ/cc.

EXAMPLE 15.

7-[2-Phenyl-2-(1-bromo-2-naphthoxy) acetamido] cephalosporanic acid:

To 680 mg. of 7-aminocephalosporanic acid in 0.7 cc. of triethylamine and 30 cc. of chloroform, was added 2-phenyl-2-(1-bromo-2-naphthoxy) acetyl chloride prepared from 1078 mg. of 2-phenyl-2-(1-bromo-2-naphthoxy) acetic acid and excess thionyl chloride and the mixture was stirred for 30 minutes under ice-cooling and then for 2 hours at room temperature. The reaction mixture was adjusted to a pH of 1.0 and the chloroform layer separated out and was condensed under reduced pressure. The remainder was washed with ether to produce 1.452 g. of a powder. This powder was refined with a mixture of acetone and ether to obtain 1.17 g. of 7-[2 - phenyl - 2 - (1 - bromo - 2 - naphthoxy) acetamido] cephalosporanic acid as a powder m.p. 85° to 89°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 224.5 mμ E 365.

MIC: *E.coli* 40 γ/cc., *St.aureus* 0.25 γ/cc.

EXAMPLE 16.

7-(2-Phenyl-3-aminomalonamido) cephalosporanic acid:

To 322 mg. of 2-phenylmalonamic acid in 15 cc. of acetone and 0.3 cc. of triethylamine was added 0.17 cc. of ethyl chloroformate at 0—5°C. and the mixture was stirred for 15 minutes. To this solution cooled to −30° to −40°C., was added drop by drop 500 mg. of 7-aminocephalosporanic acid in 16 cc. of 3% sodium bicarbonate solution in a minute, after the end of which the mixture was stirred for 30 minutes at 0° to 5°C. and then for 2 hours at room temperature. After washing twice with 50 cc. of ether, the reaction mixture was adjusted with 5% hydrochloric acid and extracted twice with 50 cc. of ethyl acetate. The ethyl acetate was distilled off under reduced pressure and the remainder dissolved in acetone and then filtered. From the filtrate, acetone was distilled off and the remainder was washed with petroleum ether to obtain 7 - (2 - phenyl - 3 - aminomalonamido) cephalosporanic acid as a faint yellow hygroscopic powder having m.p. 60° to 65°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 260 mμ, E 102.

MIC: *E.coli* >40 γ/cc., *St.aureus* 1 γ/cc.

EXAMPLE 17.

7-(2-Phenoxy-3-aminomalonamido) cephalosporanic acid:

2-Phenoxymalonamic acid (400 mg.) was dissolved in 0.2 cc. of a tetrahydrofuran solution of dicyclocarbodiimide (0.2 g/cc.) and tetrahydrofuran and the mixture was stirred for 20 minutes at room temperature. To this solution was added 500 mg. of 7-aminocephalosporanic acid and 160 mg. of sodium bicarbonate in 10 cc. of tetrahydrofuran and 10 cc. of water and the mixture was stirred for 4 hours at room temperature. To this solution was further added 2 cc. of dicyclohexylcarbodiimide and the mixture was allowed to stand overnight. The reaction mixture was filtered and from the filtrate, tetrahydrofuran was distilled off. The remaining solution was adjusted to a pH of 7.2 with

sodium bicarbonate and then filtered. The remainder was adjusted to a pH of 2.0 with hydrochloric acid and extracted with ethyl acetate. The remainder obtained by distillation of ethyl acetate was dissolved in acetone and filtered. From the filtrate, acetone was distilled off and the remainder was washed with ether to obtain 109 mg. of 7-(2-phenoxy-3-aminomalonamido) cephalosporanic acid as a powder having m.p. 100° to 110°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 269 mμ, E 158.8.

MIC: *E.coli* >40 γ/cc., *St.aureus* 5 γ/cc.

EXAMPLE 18.

7-[2-Phenyl-2-(2-naphthoxy) acetamido] cephalosporanic acid:

2 - Phenyl - 2 - (2 - naphthoxy) acetyl chloride prepared from 695 mg. of 2-phenyl-2-(2-naphthoxy) acetic acid and thionyl chloride, 680 mg. of 7-aminocephalosporanic acid and 220 mg. of sodium bicarbonate were dissolved in 30 cc. of 50% acetone and stirred for 3 hours under ice-cooling. The reaction mixture, after washing with ether, was adjusted to a pH of 2.0 with hydrochloric acid and extracted with ethyl acetate. From the extract solution ethyl acetate was distilled off and the remaining substance was washed with petroleum ether to obtain 674 mg. of 7 - [2 - phenyl - 2 - (2 - naphthoxy) acetamido] cephalosporanic acid as a powder having m.p. 85° to 100°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 234 mμ, E 141.

MIC: *E.coli* >40 γ/cc., *St.aureus* 0.5 γ/cc.

EXAMPLE 19.

7-[2-Phenyl-2-(2-ethoxyethoxy) acetamido] cephalosporanic acid:

To 165 mg. of 2-phenyl-2-(2-ethoxyethoxy)acetic acid in 10 cc. of tetrahydrofuran was added 1 cc. of a tetrahydrofuran solution containing 200 mg. of dicyclohexylcarbodiimide and the mixture was stirred for 15 minutes at room temperature. To this solution was added drop by drop 10 cc. of an aqueous solution containing 250 mg. of 7-aminocephalosporanic acid and 75 mg. of sodium bicarbonate in a minute and, after stirring for 4 hours at room temperature, the mixture was allowed to stand overnight. The reaction mixture was filtered and from the filtrate tetrahydrofuran was distilled off under reduced pressure. The remainder from which an oily decomposed compound of dicyclohexylcarbodiimide was removed, was adjusted to a pH of 1.0 with 5% hydrochloric acid and extracted with 100 cc. of ethyl acetate. From the extract solution ethyl acetate was distilled off under reduced pressure and the remainder, after dissolving in acetone, was filtered. From the filtrate, acetone was distilled off under reduced pressure and the remainder was washed with petroleum ether to obtain 100 mg. of 7-[2-phenyl-2-(2-ethoxyethoxy) acetamido] cephalosporanic acid as a white powder having m.p. 33° to 35°C. (dec.).

UV: $\lambda_{80\%\ C_2H_5OH\ .\ NaOH}^{max}$ 260 mμ, E 101.

MIC: *E.coli* >40 γ/cc., *St.aureus* 2 γ/cc.

EXAMPLE 20.

7-(2-Phenoxy-2-ethoxycarbonylacetamido) cephalosporanic acid:

To 403 mg. of 2-phenoxy-2-ethoxycarbonylacetic acid in 10 cc. of tetrahydrofuran was added 2 cc. of a tetrahydrofuran solution containing 400 mg. of dicyclohexylcarbodiimide and the mixture was stirred for 15 minutes at room temperature. To this solution was added 10 cc. of an aqueous solution containing 500 mg. of 7-aminocephalosporanic acid and 150 mg. of sodium bicarbonate and, after stirring for 3 hours, the mixture was allowed to stand overnight. The reaction mixture was filtered and from the filtrate tetrahydrofuran was distilled off under reduced pressure. The remainder from which an oily decomposed compound of dicyclohexylcarbodiimide was removed, was adjusted to a pH of 1.0 with 5% hydrochloric acid and extracted with 100 cc. of ethyl acetate. From the extract solution ethyl acetate was distilled off under reduced pressure and the remainder was dissolved in acetone and then filtered. From the filtrate, acetone was distilled off under reduced pressure and the remainder was washed with a mixture of ether and petroleum ether to obtain 42 mg. of 7 - (2 - phenoxy - 2 - ethoxycarbonylacetamido) cephalosporanic acid as a powder having m.p. 120° to 128°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 267 mμ, E 188.

MIC: *E.coli* >40 γ/cc., *St.aureus* 2 γ/cc.

EXAMPLE 21.

7-[2-Phenyl-2-(phenylthio) acetamido] cephalosporanic acid:

To 490 mg. of 2-phenyl-2-(phenylthio) acetic acid dissolved in 15 cc. of tetrahydrofuran was added 2 cc. of a tetrahydrofuran solution containing 214 mg. of dicyclohexylcarbodiimide and the mixture was stirred for 30 minutes at room temperature. To this solution was added drop by drop 540 mg. of 7-aminocephalosporanic acid and 180 mg. of sodium bicarbonate in 5 cc. of water and 5 cc. of tetrahydrofuran in a minute and the mixture was stirred for 6 hours at room temperature. The reaction mixture was filtered and from the filtrate tetrahydrofuran was distilled off under reduced pressure. The remaining solution was filtered and after adjusting the solution to a pH of 2.0 with 5% hydrochloric acid, the filtrate was extracted with 100 cc. of ethyl acetate. From the extract solution, ethyl acetate was distilled off under reduced pressure and the remainder was washed with a mixture of ether and ligroin to obtain 40 mg. of 7-[2-phenyl-2-(phenylthio) acetamido] cephalosporanic acid as a powder having m.p. 114° to 120°C. (dec.).

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 260 mμ, E 298.

MIC: *E.coli* >40 γ/cc., *St.aureus* 0.2 γ/cc.

EXAMPLE 23.

7-{2-Phenyl-2-[*o*-methoxy-*p*-(2-propenyl) phenoxy] acetamido} cephalosporanic acid:

7-Aminocephalosporanic acid (540 mg.) and 170 mg. of sodium bicarbonate were dissolved in 10 cc. of water and 10 cc. of tetrahydrofuran. To this solution was added 1185 mg. of 2 - phenyl - 2 - [*o* - methoxy - *p* - (2-propenyl) phenoxy] acetic acid dissolved in 15 cc. of tetrahydrofuran and 2 cc. of a tetrahydrofuran solution of dicyclohexylcarbodiimide (0.2 g/cc.), and the mixture was stirred for 3 hours at room temperature. The reaction mixture was filtered and the filtrate was condensed under reduced pressure, after which the condensed solution was further filtered. The resulting filtrate was adjusted to a pH of 2 with hydrochloric acid and extracted with ether. The extract solution was condensed under reduced pressure and the remainder was dissolved in ether. The ether solution was condensed under reduced pressure and the condensed solution was filtered. The filtrate was further condensed to obtain 432 mg. of 7 - {2-phenyl - 2 - [*o* - methoxy - *p* - (2 - propenyl) phenoxy) acetamido} cephalosporanic acid as a hygroscopic powder.

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 275 mμ, E 153.

MIC: *E.coli* >40 γ/cc., *St.aureus* 1 γ/cc.

EXAMPLE 24.

DL-7-[2-phenyl-3-(*p*-methoxyphenyl) propionamido] cephalosporanic acid

7-Aminocephalosporanic acid (4.3 g.) was dissolved in 80 cc. of chloroform and 5 cc. of triethylamine and stirred under ice-cooling. To this solution was added drop by drop a chloroform solution containing DL-2-phenyl-3-(*p*-methoxyphenyl) propionyl chloride over 30 minutes and the mixture was stirred for an hour and then for 3 hours at room temperature. To the reaction mixture was added water and the mixture was adjusted to a pH of 1.0 with 10% hydrochloric acid. The chloroform layer was washed with water and dried over magnesium sulphate, after which chloroform was distilled off under reduced pressure. The remainder was washed with ether and petroleum ether and the resulting crude crystals (7.27 g.) were recrystallised from water and ethanol to obtain 3.87 g. of DL-7 - [2 - phenyl - 3 - (*p* - methoxyphenyl) propionamido] cephalosporanic acid as crystals having m.p. 104°C. (dec.).

MIC: *E.coli* 40 γ/cc., *St.aureus* 1.25 γ/cc.

EXAMPLE 22.

7-[2,2-Di(phenylthio) acetamido] cephalosporanic acid:

2,2-Di(phenylthio)acetic acid (500 mg.) and 426 mg. of dicyclohexylcarbodiimide were dissolved in 10 cc. of tetrahydrofuran and stirred for 20 minutes at room temperature. To this solution was added 500 mg. of 7-aminocephalosporanic acid and 160 mg. of sodium bicarbonate in 10 cc. of tetrahydrofuran and 10 cc. of water and the mixture was stirred for 5 hours at room temperature. To this solution was further added 1 cc. of dicyclohexylcarbodiimide solution and the mixture was allowed to stand overnight. The reaction mixture was filtered and from the filtrate tetrahydrofuran was distilled off under reduced pressure. The remaining solution was adjusted to a pH of 7.2 with sodium bicarbonate and then filtered. The remainder was adjusted to a pH of 2.0 with hydrochloric acid and extracted with etheyl acetate. From the extract solution, ethyl acetate was distilled off and the remainder was washed with ether to obtain 93 mg. of 7-[2,2-di(phenylthio) acetamido] cephalosporanic acid as a powder having m.p. 78° to 85°C. (dec.).

Analysis:

Calculated for $C_{26}H_{26}O_7N_2S.H_2O$ C 59.08, H 5.34, N 5.30, S 6.07,
Found C 59.48, H 5.59, N 5.56, S 6.25.

UV: $\lambda_{max}^{80\%\ C_2H_5OH\ .\ NaOH}$ 226 mμ E 371; 265, 176.

MIC: *E.coli* >40 γ/cc., *St.aureus* 2 γ/cc.

EXAMPLE 25.

7-(2-Chloro-2-phenylacetamido)-3-pyridinium methyl-decephalosporanic acid inner salt:

7 - (2 - Chloro - 2 - phenylacetamido) cephalosporanic acid obtained as in Example 1. (100 mg.) was dissolved in 2 cc. of pyridine and 3 cc. of water and allowed to stand for 30 hours at 37° to 40°C. in a current of nitrogen gas, while shaking 3 or 4 times. After the reaction was over the reaction mixture was treated with 3 cc. of ethyl acetate twice and the water layer was condensed under reduced pressure. The residue was dissolved in water and purified through a column packed with an anion exchange resin (Dowex-1). The eluate was solidified by dry-freezing to obtain 15 mg. of 7 - (2 - chloro - 2 - phenylacetamido) - 3 - pyridinium methyl - decephalosporanic acid inner salt.

Electrophoresis: −22 mm (14 volt/cm . 3 hours)

UV: $\lambda_{max}^{80\%\ C_2H_5OH}$ 260 mμ, E 135.

MIC: *E.coli* 40 γ/cc., *St.aureus* 1 γ/cc.

EXAMPLE 26.

7-(2-Bromo-2-phenylacetamido)-3-pyridinium methyl decephalosporanic acid inner salt:

7 - Amino - 3 - pyridinium methyl - decephalosporanic acid inner salt and 2-bromo-2-phenylacetyl chloride in 50% acetone were treated in the presence of sodium bicarbonate in the same way as described in Example 2. The reaction mixture was treated with ether at a pH of 5.5 to 6.5 and the water layer was purified through a column packed with Dowex-1. The solution containing the desired compound was condensed under reduced pressure and added to acetone to obtain the desired compound.

Electrophoresis: −27 mm (14 volt/cm . 3 hours)

EXAMPLE 27.

7-(2-Phenyl-3-*p*-methoxyphenylpropionamido)-3-pyridinium methyl-decephalosporanic acid inner salt:

7 - Amino - 3 - pyridinium methyl - decephalosporanic acid inner salt and 2-phenyl-3-*p*-methoxyphenylpropionyl chloride were treated in the same way as described in Example 26. m.p. 180°C. (dec.).

EXAMPLE 28.

7-(2-Phenyl-3-*p*-methoxyphenylpropionamido)-3-(1-imidazolinium) methyl-decephalosporanic acid inner salt:

7 - Amino - 3 - (1 - imidazolinium) methyl-decephalosporanic acid inner salt and 2-phenyl - 3 - *p* - methoxyphenylpropionyl chloride were treated in the same way as described in Example 26. m.p. 65°—70°C.

UV: $\lambda_{max}^{H_2O}$ 276 mμ, E 47.

MIC: *E.coli* >40 γ/cc., *St.aureus* 2.5 γ/cc.

EXAMPLE 29.

7-(2-Phenyl-3-*p*-methoxyphenylpropionamido)-3-[1-(2-methyl) imidazolinium] methyl-decephalosporanic acid inner salt:

7 - Amino - 3 - [1 - (2 - methyl) imidazolinium] methyl-decephalosporanic acid inner salt and 2-phenyl-3-*p*-methoxyphenylpropionyl chloride were treated in the same way as described in Example 26.

MIC: *E.coli* >40 γ/cc., *St.aureus* 2.5 γ/cc.

EXAMPLE 30.

7-(2-Phenyl-3-*p*-methoxyphenylpropionamido)-3-[1-(2-amino) pyridinium] methyl-decephalosporanic acid inner salt:

7 - Amino - 3 - [1 - (2 - amino) pyridinium] methyl-decephalosporanic acid inner salt and 2-phenyl-3-*p*-methoxyphenylpropionyl chloride were treated in the same way as described in Example 26.

MIC: *E.coli* >40 γ/cc., *St.aureus* 4 γ/cc.

EXAMPLE 31.

Dicyclohexylamine salt of 7-(2-chloro-2-phenylacetamido) cephalosporanic acid:

To an aqueous solution of the substance obtained in Example 1 was added drop by drop an acetone solution of dicyclohexylamine at room temperature under vigirous stirring and the mixture was allowed to stand in an ice-box to obtain the dicyclohexylamine salt of 7 - (2 - chloro - 2 - phenylacetamido) cephalosporanic acid having m.p. 196° to 200°C. which was recrystallised from alcohol and water.

UV: $\lambda_{max}^{2\%\ HCON(CH_3)_2 . H_2O}$ 257 mμ, E 112.

EXAMPLE 32.

Dibenzylethylenediamine salt of 7-(2-chloro-2-phenylacetamido) cephalosporanic acid:

The substance obtained in Example 1 and dibenzylethylenediamine were treated in the same way as described in Example 31 to obtain the dibenzylethylenediamine salt of 7 - (2 - chloro - 2 - phenylacetamido) cephalosporanic acid having m.p. 171° to 174°C. (dec.).

EXAMPLE 33.

Sodium salt of 7-(2-chloro-2-phenylacetamido) cephalosporanic acid:

The substance obtained in Example 1 and sodium bicarbonate were treated in the same way as described in Example 31 to obtain the sodium salt of 7-(2-chloro-2-phenylacetamido) cephalosporanic acid.

UV: $\lambda_{max}^{H_2O}$ 260 mμ, E 208.

EXAMPLE 34.

Dicyclohexylamine salt of 7-(2-bromo-2-phenylacetamido) cephalosporanic acid:

The substance obtained in Example 2 and dicyclohexylamine were treated in the same way as described in Example 31 to obtain the dicyclohexylamine salt of 7-(2-bromo-2-phenylacetamido) cephalosporanic acid m.p. 159° to 165°C. (dec.)

UV: $\lambda_{inf.}^{20\%\ Tetrahydrofuran . H_2O}$ 258—263 mμ, E 158.

EXAMPLE 35.

Dibenzylethylenediamine salt of 7-(2-bromo-2-phenylacetamido) cephalosporanic acid:

The substance obtained in Example 2 and dibenzylethylenediamine were treated in the same way as described in Example 31 to obtain the dibenzylethylenediamine salt of 7 - (2 - bromo - 2 - phenylacetamido) cephalosporanic acid m.p. 150° to 153°C. (dec.).

UV: $\lambda_{max}^{2\%\ HCON(CH_3)_2 . H_2O}$ 257 mμ, E 142.

EXAMPLE 36.

Sodium salt of 7-(2-bromo-2-phenylacetamido) cephalosporanic acid:

The substance obtained in Example 2 and sodium bicarbonate were treated in the same way as described in Example 31 to obtain the sodium salt of 7 - (2 - bromo - 2 - phenylacetamido) cephalosporanic acid.

UV: End_{min} (H_2O), $\lambda_{inf}^{H_2O}$ 259—264 mμ, E 191.

EXAMPLE 37.

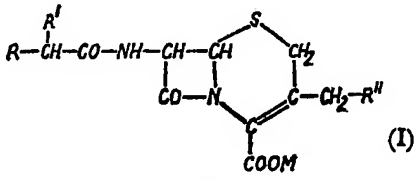
7-(2-Bromo-2-phenylacetamido)-3-pyridinium methyl decephalosporanic acid inner salt:

The substance obtained in Example 2 and pyridine were treated in the same way as described in Example 25 to obtain 7 - (2-bromo - 2 - phenylacetamido) - 3 - pyridinium methyl - decephalosporanic acid inner salt.

Electrophoresis: −27 mm (14 volt/cm . 3 hours).

WHAT WE CLAIM IS:—

1. A 7-(α-substituted acylamino) cephalosporanic acid or a derivative thereof having the general formula



(I)

wherein R is a halogen atom or an azido (N_3), carbamoyl, lower alkylthio, lower alkanoyl, lower alkanoxyloxy, lower alkoxy-lower alkoxy, lower alkoxy-aralkyl, naphthoxy, halonaphthoxy, ethoxycarbonyl, arylthio or haloarylthio group or a phenoxy group having lower alkenyl and lower alkoxy substituents, R′ is an aryl, haloaryl, nitroaryl, aryloxy or arylthio group, R″ is an

acetoxy, pyridinium, aminopyridinium, imidazolinium or methylimidazolinium group, and M is a hydrogen atom, a pharmaceutically acceptable non-toxic cation or an anionic charge.

2. 7 - (2 - Chloro - 2 - phenylacetamido) cephalosporanic acid.

3. 7 - (2 - Bromo - 2 - phenylacetamido) cephalosporanic acid.

4. 7 - [2 - Chloro - 2 - (*p* - chlorophenyl) acetamido] cephalosporanic acid.

5. 7 - [2 - Chloro - 2 - (*p* - bromophenyl) acetamido] cephalosporanic acid.

6. 7 - [2 - Bromo - 2 - (*p* - chlorophenyl) acetamido] cephalosporanic acid.

7. 7 - [2 - Chloro - 2 - (*p* - nitrophenyl) acetamido] cephalosporanic acid.

8. 7 - [2 - Bromo - 2 - (1 - naphthyl) acetamido] cephalosporanic acid.

9. 7 - [2 - Azido - 2 - (*p* - chlorophenyl) acetamido] cephalosporanic acid.

10. 7 - [2 - Azido - 2 - (*p* - nitrophenyl) acetamido] cephalosporanic acid.

11. 7 - (2 - Acetoxy - 2 - phenylacetamido) cephalosporanic acid.

12. 7 - (2 - Methylthio - 2 - phenylacetamido) cephalosporanic acid.

13. 7 - (2 - Acetyl - 2 - phenylacetamido) cephalosporanic acid.

14. 7 - (2 - Propylthio - 2 - phenylacetamido) cephalosporanic acid.

15. 7 - [2 - Phenyl - 2 - (*o* - bromophenylthio) acetamido] cephalosporanic acid.

16. 7 - [2 - Phenyl - 2 - (1 - bromo - 2-naphthoxy)acetamido] cephalosporanic acid.

17. 7 - (2 - Phenyl - 3 - aminomalonamido) cephalosporanic acid.

18. 7 - (2 - Phenoxy - 3 - amino - malonamido) cephalosporanic acid.

19. 7 - [2 - Phenyl - 2 - (2 - naphthoxy)-acetamido] cephalosporanic acid.

20. 7 - [2 - Phenyl - 2 - (2 - ethoxyethoxy) acetamido] cephalosporanic acid.

21. 7 - (2 - Phenoxy - 2 - ethoxycarbonylacetamido) cephalosporanic acid.

22. 7 - (2 - Phenyl - 2 - phenylthioacetamido) cephalosporanic acid.

23. 7 - [2,2 - Di(phenylthio)acetamido] cephalosporanic acid.

24. 7 - {2 - Phenyl - 2 - [*o* - methoxy-*p*-(2 - propenyl) phenoxy] acetamido} cephalosporanic acid.

25. DL - 7 - [2 - phenyl - 3 - (*p* - methoxyphenyl) propionamido] cephalosporanic acid.

26. 7 - (2 - Chloro - 2 - phenylacetamido)-3 - pyridinium methyldecephalosporanic acid inner salt.

27. 7 - (2 - Bromo - 2 - phenylacetamido)-3 - pyridinium methyl - decephalosporanic acid inner salt.

28. 7 - (2 - Phenyl - 3 - *p* - methoxyphenylpropionamido) - 3 - pyridinium methyldecephalosporanic acid inner salt.

29. 7 - (2 - Phenyl - 3 - *p* - methoxyphenylpropionamido) - 3 - (1 - imidazolinium) - methyl - decephalosporanic acid inner salt.

30. 7 - (2 - Phenyl - 3 - *p* - methoxyphenylpropionamido) - 3 - [1 - (2 - methyl)-imidazolinium] methyl - decephalosporanic acid inner salt.

31. 7 - (2 - Phenyl - 3 - *p* - methoxyphenylpropionamido) - 3 - [1 - (2 - amino) pyridinium] methyl - decephalosporanic acid inner salt.

32. Dicyclohexylamine salt of 7 - (2-chloro - 2 - phenylacetamido) - cephalosporanic acid.

33. Dibenzylethylenediamine salt of 7-(2 - chloro - 2 - phenylacetamido) cephalosporanic acid.

34. Sodium salt of 7 - (2 - chloro - 2-phenylacetamido) cephalosporanic acid.

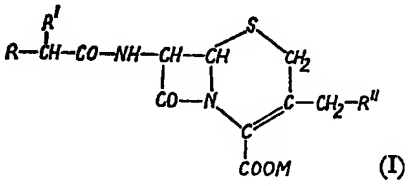
35. Dicyclohexylamine salt of 7 - (2-bromo - 2 - phenylacetamido) cephalosporanic acid.

36. Dibenzylethylenediamine salt of 7-(2 - bromo - 2 - phenylacetamido) cephalosporanic acid.

37. Sodium salt of 7 - (2 - bromo - 2-phenylacetamido) cephalosporanic acid.

38. 7 - (2 - Bromo - 2 - phenylacetamido)-3 - pyridinium methyldecephalosporanic acid inner salt.

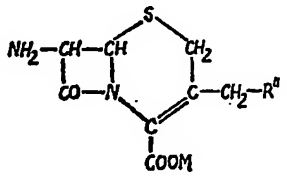
39. A process of preparing a 7-(α-substituted acylamino) cephalosporanic acid or a derivative thereof having the general formula:



(I)

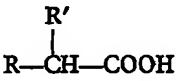
wherein R is a halogen atom or an azido (N_3), carbamoyl, lower alkylthio, lower alkanoyl, lower alkanoyloxy, lower alkoxy-lower alkoxy, lower alkoxy-aralkyl, naphthoxy, halonaphthoxy. ethoxycarbonyl arylthio or haloarylthio group or a phenoxy group having lower alkenyl and lower alkoxy substituents, R′ is an aryl, haloaryl, nitroaryl, aryloxy or arylthio group, R″ is an acetoxy, pyridinium, aminopyridinium, imidazolinium or methylimidazolinium group and M is a hydrogen atom, a pharmaceutically acceptable non-toxic cation or an anionic charge,

which comprises reacting 7-aminocephalosporanic acid or a derivative thereof having the general formula:



(II)

wherein R'' and M are as defined above, with an α-substituted carboxylic acid having the general formula



(III)

wherein R and R' are as defined above or a reactive derivative thereof, and, if desired, treating the resulting compound with an alkali metal hydroxide, alkali metal salt of a higher fatty acid or an organic amine to produce a pharmaceutically acceptable non-toxic cation salt thereof.

40. A process according to claim 39, wherein a compound having the formula (I) in which R'' is acetoxy is first prepared and is then reacted with pyridine, aminopyridine, imidazole or methylimidazole to form the corresponding compound in which R'' is pyridinium, aminopyridinium, imidazolinium or methylimidazolinium.

41. A process according to claim 39, wherein the reaction is carried out in a solvent which is inert in the reaction.

42. A process for preparing a compound of formula (I) herein, substantially as hereinbefore described with reference to the Examples.

43. A 7-(α-substituted acylamino) cephalosporanic acid and derivatives thereof having formula (I) herein whenever prepared by a process according to any one of claims 39 to 42.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.